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A Brief Review on Solubility Enhancement Techniques with Drug and Polymer

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ABSTRACT: The process of a solid dissolving in a liquid phase to create a homogenous mixture is known as solubility. A crucial factor in getting the right quantity of drug into the bloodstream to show a pharmacological effect is solubility. The main issue in developing formulations for new chemical entities as well as for the creation of generics is low water solubility. More than 40% of novel chemical entities (NCEs) created in the pharmaceutical sector are essentially water insoluble. For formulation scientists, solubility is a significant challenge. Any medicine that is to be absorbed at the absorption site must be there in solution form. The solubility of pharmaceuticals that are poorly soluble can be improved using a variety of approaches, such as complexation, salt formation, particle size reduction, crystal engineering, salt formation, solid dispersion, and the like. The choice of a solubility-improving technology is influenced by pharmacological properties, absorption sites, and the requirements for the dosage form. This review article's goal is to improve bioavailability and promote effective absorption.

KEY WORDS: Bioavailability, Nanosuspensions, Dispersion, Solubility. Supercritical fluid.

INTRODUCTION

A chemical compound's solubility is its capacity to dissolve in a solid, liquid, or gaseous solvent to produce a homogenous solution of the solute in the solvent. Fundamentally, the solubility of a chemical depends on the solvent employed as well as on temperature and pressure. The saturation concentration, at which more solute cannot raise the concentration of the substance, is used to gauge how soluble a chemical is in a certain solvent. Poorly water-soluble medications can benefit from a range of strategies to improve their solubilization and bioavailability. Medicine is frequently dissolved in solutions using a variety of techniques, including micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellarsolubilization, hydrotropy, and others.

In novel chemical entity screening investigations as well as formulation design and development, the solubilization of pharmaceuticals with poor solubility is a frequent challenge. As a result of the simultaneous and conflicting processes of dissolving and phase joining (such as the precipitation of solids), solubility happens under dynamic equilibrium. When the two processes move forward at a constant rate, soluble equilibrium happens.

Under specific circumstances, equilibrium solubility may be exceeded, producing a metastable substance known as a supersaturated solution. Solubility is the maximum amount of analyte that can be dissolved in a volume of solvent. It has both quantitative and qualitative characteristics[1-2]

Some instrument used for enhance the solubility of drug and pharmaceutical formulation likeMicronization, Hot-Melt Method, SCF, Spray Freezing into Cryogenic Liquids, Lyophilization/Freeze-Drying Technique, Microwave Irradiation Method[3]

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1. Biopharmaceutical Classification System

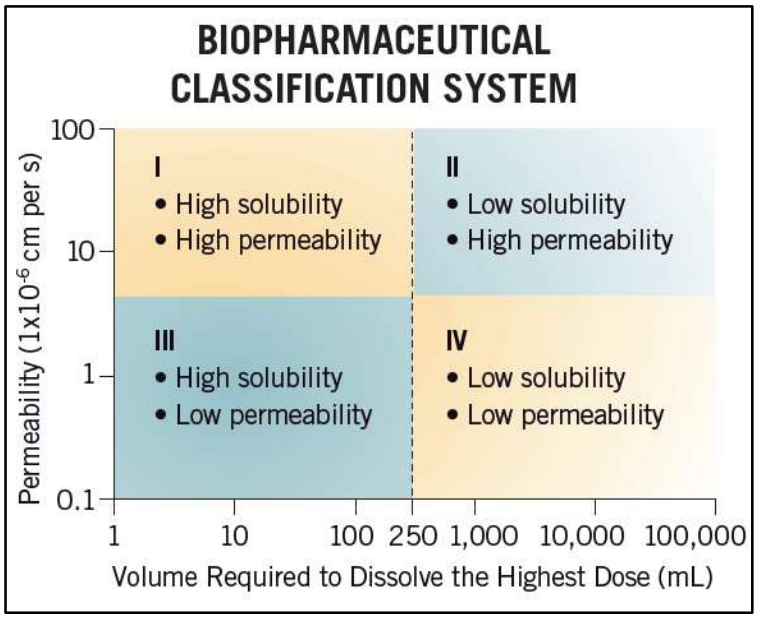

Fig 1 : Biopharmaceutical Classification System

In terms of water solubility and intestinal permeability, the BCS is a scientific paradigm for classifying medications. The BCS takes into account three critical variables, including solubility, intestinal permeability, and dissolution rate, along with the drug product's in vitro dissolving characteristics. These variables all have an impact on the rate and volume of oral drug absorption from sudden release solid oral-dosage forms[4-5].

Based on their solubility and permeability, medicines are divided into four basic classes by the US Food & Drug Administration (FDA), according to the BCS.

Class Ist

It has a high absorption and dissolution number. Bioavailability and dissolution are extremely fast. As a result, bioavailability and bioequivalency studies are not required for this product.

Class IInd

The medications have a high absorption rate but a low disintegration rate. Except at very high dose numbers, in vivo drug dissolution is a rate limiting step for absorption. The medication has inconsistent bioavailability and requires improvement.

Class IIIrd

The permeability of the drug is the rate limiting step in drug absorption. The pace and amount of medication absorption in these medicines varies greatly. Because the dissolution is quick, The difference is due to changes in physiology and membrane permeability rather than dose form variables. These medicines are difficult to create for regulated release. These drugs demonstrated low bioavailability and require permeability enhancement.

Class IVth

The medications' bioavailability is weak and varied. Several parameters, including dissolving rate, permeability, and stomach emptying, serve as rate limiting processes in medication absorption[6].

2. The significance of lubricity:

Due to its simplicity, high patient compliance, cost effectiveness, lack of sterility restrictions, and flexibility in dosage form design, oral consumption is the most practical and frequently used method of drug delivery. Because of this, many generic medication manufacturers are more likely to produce bioequivalent oral drug formulations[7]. The oral bioavailability is influenced by a number of variables, such as the drug's aqueous solubility, permeability to water, rate of dissolution, first-pass metabolism, presystemic metabolism, and sensitivity to efflux mechanisms.Low permeability and poor solubility are the most frequent causes of

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low oral bioavailability. Therefore, increasing the solubility of BCS Class II & Class IV medicines also increases their bioavailability[8].

3. Techniques for Increasing Solubility:

Techniques used to increase solubility can be divided into two categories: physical modifications and chemical changes to the medicinal ingredient bodily alterations. Drug dispersion in carriers such as eutectic mixes, solid dispersions, solid solutions, and cryogenic procedures.Modification of the crystal habit such as polymorphs, amorphous form, and cocrystallization.Chemical alterations.Derivatization, complexation, usage of a buffer, and salt production. Various Techniques using a supercritical fluid technique, solubilizers, co solvency, hydrotrophy, and new excipients as adjuvants[9].

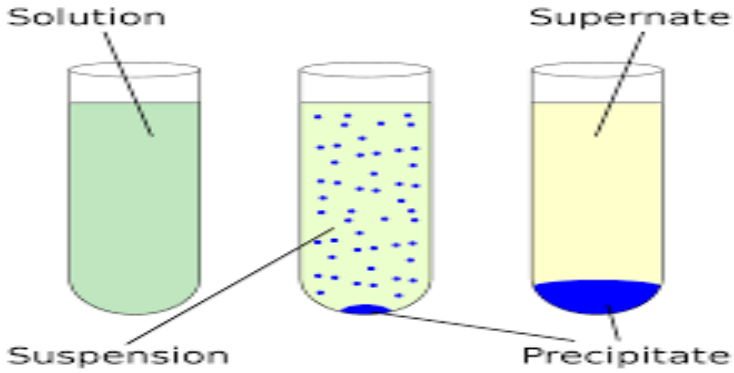

Fig 2: Techniques for Increasing Solubility

4. Reducing Particle Size:

Drug particle size has a strong inverse relationship with solubility; as a particle gets smaller, its surface area to volume ratio rises. Greater contact between the surface and the solvent is made possible by the bigger surface area, increasing solubility.

The active ingredient is disaggregated by mechanical stress in conventional particle size reduction techniques including comminution and spray drying. Thus, solubility augmentation is now possible through an effective, repeatable, and affordable method thanks to particle size reduction. However, the physical stress that is frequently applied to the therapeutic product during comminution processes like milling and grinding could lead to degradation. When processing thermosensitive or unstable active chemicals, the thermal stress that may develop during comminution and spray drying is also a concern. Traditional methods may not be able to increase the solubility of nearly insoluble pharmaceuticals to the necessary degree[10-11].

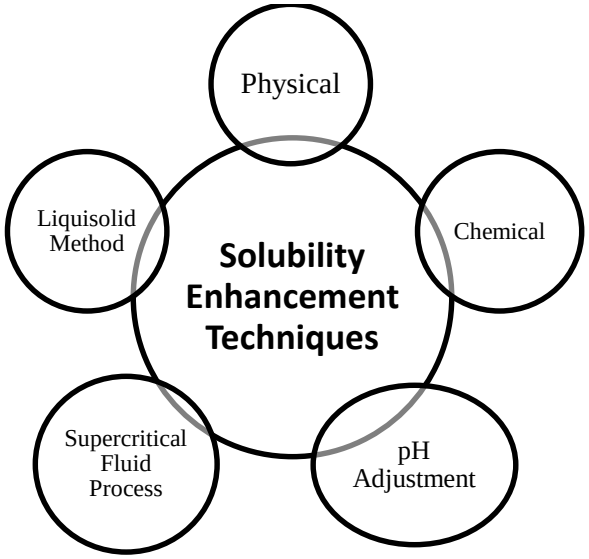

Fig 3: Broad Classification of Solubility Enhancement Techniques

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Advantages and Disadvantages:

1. Benefits Produces homogeneous particles with a limited variety of particle sizes and increases surface area.
2. Amorphous or disordered regions are present in the final product as a result of the high energy procedure, which disrupts the drug's crystal structure. Because these regions are thermodynamically unstable, they are prone to recrystallization when stored in hot and humid environments.
3. This method, known as nanosuspension, is used to disperse medications that are poorly soluble in water and oils.
4. Nanosuspension is a biphasic system made up of nanoparticles suspended in water.
5. Nano size medication particles are stabilised by surfactant for parenteral and pulmonary delivery[10-11].

5. Particle Dispersion:

When Sekiguchi and Obi examined the production and efficacy of eutectic melts of a sulfonamide medication and a water-soluble carrier in the early 1960s they first put up the idea of solid dispersions. Solid dispersions are a practical pharmaceutical approach for enhancing the drug dosage forms' ability to dissolve, absorb, and deliver therapeutic effects. Generally speaking, a hydrophilic matrix and a hydrophobic medication make up a solid dispersion, which is a collection of solid products made up of at least two separate ingredients. Polyvinylpyrrolidone (Povidone, PVP), polyethylene glycols (PEGs), and PlasdoneS630 are the most often utilised hydrophilic carriers for solid dispersions.

The creation of solid dispersion also involves the use of surfactants such Tween-80, sodium docusate, Myrj-52, Pluronic-F68, and sodium lauryl sulphate (SLS)[12].

6. Process Using Supercritical Fluid (SCF):

Supercritical fluids (SCFs) can dissolve non-volatile solvents near the critical point of carbon dioxide. A SCF is a single phase above its critical temperature and pressure. It is secure, economical, and environmentally friendly. Due to their favourable operating conditions, SCFs are attractive for pharmacological research (temperature and pressure). SCFs, which are intermediate between pure liquid and pure gas, have characteristics that are helpful in the processing of products. Additionally, close to the critical points, minute variations in operating temperature, pressure, or both have an impact on density, transport properties (such viscosity and diffusivity), and other physical characteristics (such as dielectric constant and polarity). Common supercritical solvents include carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water. The SCF techniques' flexibility and precision enable the micronization of medication particles within certain particle size ranges, frequently to submicron levels.

The ability to produce nanoparticulate suspensions of particles with a diameter of 5-2,000 nm has been established by current SCF methods. In order to reduce particle size and improve solubility, a number of pharmaceutical companies, including Nektar Therapeutics and Lavipharm, are focusing in particle engineering. Precipitation with compressed antisolvent process (PCA), solution enhanced dispersion by SCF (SEDS), supercritical antisolvent processes (SAS), rapid expansion of supercritical solutions (RESS), gas anti solvent recrystallization (GAS), and aerosol supercritical extraction system are some of the SCF processing techniques that have been developed to address specific aspects of these shortcomings[12-13].

7. Liquisolid Techniques:

Both absorption and adsorption happen when a drug dissolved in a liquid vehicle is added to a carrier substance with a porous surface and fibres inside, like cellulose. Specifically, the liquid first absorbs into the interior of the particles and is captured by its internal structure, and once this process reaches saturation, the liquid is adsorption onto the internal and external surfaces of the porous carrier particles. A liquid drug can be transformed into a dry, non-adherent, free-flowing, compressible powder by mixing it with certain powder excipients, like the carrier and coating substance. Amorphous and microcrystalline cellulose as well as silica powders are used as coating materials[14].

8. Complex Formation-Based Techniques Inclusion:

The inclusion complex creation technique has been used more accurately than any other solubility enhancement method to increase the aqueous solubility, dissolving rate, and bioavailability of medicines that are not very water soluble. The nonpolar

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molecule or nonpolar area of one molecule (referred to as the guest) is inserted into the cavity of another molecule or group of molecules to produce inclusion complexes (known as host). Cyclodextrins are the most popular host molecules. Cyclodextrins are produced as a result of the enzymatic breakdown of starch.

Although the cyclodextrin molecules are water soluble due to their surface, the hydrophobic cavity offers a habitat for non-polar molecules of the right size. Depending on the characteristics and structure of the drug molecule, 1: 1 or 1: 2 drugs can be produced. Complex cyclodextrin.[15]

Table 1: Solubility Enhancement Techniques with drug and polymer

Sr .No.	Solubility Enhancement Techniques	Drug	Polymer
1	Reducing Particle Size	Griseofulvin, progesterone, spironolactone diosmin, and fenofibrate	(Povidone, PVP), polyethylene glycols (PEGs), and PlasdoneS630[16-17]
2	Solid Dispersion	celecoxib, halofantrine, and ritonavir	polyvinylpyrrolidone (Povidone, PVP), polyethylene glycols (PEGs), PlasdoneS630. Surfactants like Tween-80, docusate sodium, Myrj-52, Pluronic-F68, and sodium lauryl sulphate (SLS)[16-17]
3	Melt Evaporation, Lyophillization	Fenofibrate	PEG6000, Poloxamer 407
4.	Fusion (Melt) Method	Glipizide	Mannitol, PVPK30
5.	Solvent evaporation method	Flurbiprofen	HPC
6.	Co- precipitation	Chlordiazepoxide	Mannitol, PVPK30[18]

CONCLUSION

In this review article, we draw the conclusion that every molecule's solubility is essential and has a big impact on how medicines are developed and formulated. Medication dissolution determines the rate of weakly water-soluble drug oral absorption, and solubility is also a key factor in the formulation and development of various dosage forms of various drugs. Poorly water-soluble medications are absorbed from the mouth at a pace determined by drug dissolution, and solubility is a necessary condition for ingestion. The various methods outlined above can be employed singly or in combination to increase the medications' solubility in the GIT. The type and qualities of the medicine, such as its chemical composition, physical nature, pharmacokinetic behaviour, and other characteristics, influence the method of boosting solubility that is chosen. It is now possible to improve the solubility of drugs that aren't very soluble by employing a variety of techniques, such those mentioned above.

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